sectioning and efficiency observed with the use of medium "C" may argue for its value and preferential utilization despite similar overall readability among products. Other considerations regarding selection of a particular medium may include cost, with medium "B" being least expensive and medium "A" being most, among the media considered.[8] Further studies are necessary to understand how these media may vary in their propensity to induce particular types of histologic artifacts or their utility for particular types of tissue specimens.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Ideal Mohs frozen section with overall readability score (ORS) of 10 (hematoxylin and eosin, original magnification ×2).

Reflectance confocal microscopy for the diagnosis of Galli-Galli disease

Reflectance confocal microscopy (RCM) has already been described for the diagnosis of some inflammatory skin diseases.[1] This novel technique offers examination with cellular resolution up to 250 μm in depth. Hence, RCM has the potential of being a complementary tool for the diagnosis of epidermal dermatoses that might include suprabasal acantholytic diseases, which are known for their clinical heterogeneous presentation.[2]

A 48-year-old woman presented with a 4-year history of a recurrent, pruritic, and symmetrical papular eruption on her lower limbs, chest, and arms, worsened with heat exposure. She also mentioned a simultaneous, progressive, asymptomatic macular hyperpigmentation involving the chest and neck. Her past medical history was unremarkable. She had no family history of a similar condition. Physical examination revealed multiple erythematous, follicular, and hyperkeratotic papules (Fig. 1a). They were interspaced by lentigo-like macules on the chest and neck (Fig. 1b).

Dermoscopy of a hyperkeratotic papule showed a central brown, mottled area surrounded by a whitish halo (Fig. 1c), while dermoscopy of a lentigo-like macule disclosed a peripheral pseudoreticular pattern, reminiscent of moth-eaten borders, and a central brown homogenous area (Fig. 1d).

Further RCM examination was performed. Imaging of a hyperkeratotic papule at epidermal level revealed focal dark clefts with multiple bright, roundish cells within (Fig. 2a). RCM imaging of a lentigo-like macule allowed the observation at the dermal–epidermal junction of multiple, branched, deer antler-like highly refractile structures (Fig. 2b).

Figure 1 Galli-Galli disease – clinical and dermoscopic presentation. (a) Symmetrical distribution of multiple erythematous, hyperkeratotic, follicular papules on the lower limbs. (b) They are also observed on the chest and neck interspaced by numerous, confluent lentigo-like macules. No pitted perioral scars or comedo-like lesions were seen. (c) Dermoscopy of a hyperkeratotic papule (leg): central brown, mottled area (black square) surrounded by a whitish halo (red arrows), which correspond to compact hyperkeratosis and acantholysis, respectively. Mirroring its clinical appearance, the dermoscopic features of hyperkeratotic papules (in Galli-Galli disease) also resemble Grover's disease. (d) Dermoscopy of a lentigo-like macule (chest): peripheral pseudoreticular pattern

Clinical and dermoscopic appearance correlated to *in vivo* confocal features of intraepidermal acantholysis and elongated rete ridges, suggesting the diagnosis of Galli-Galli disease, which was confirmed after punch biopsy. Histopathological examination is detailed in Figure 2c.

Reflectance confocal microscopy has already been described for the diagnosis of few acantholytic skin diseases, including Darier disease and Hailey-Hailey disease.[3,4] GGD is a very rare acantholytic variant of Dowling-Degos disease. It can occur sporadically, as exemplified by our patient.[5] We showed that dermoscopy and RCM may provide important clues for the diagnosis of GGD, when adequately integrated to clinical data. Epidermal dark clefts and round bright cells seen in RCM correlate well to suprabasal acantholysis and dyskeratotic keratinocytes, respectively. Characteristic elongated rete ridges have an excellent correlation to the confocal deer antler-like bright structures and lentigo-like dermoscopic presentation.

As GGD is also recognized as an autosomal dominant genodermatosis, knowledge of such *in vivo* features will not only allow an early diagnosis but also potentially reduce the need for other invasive procedures when examining multiple affected patients of the same family.

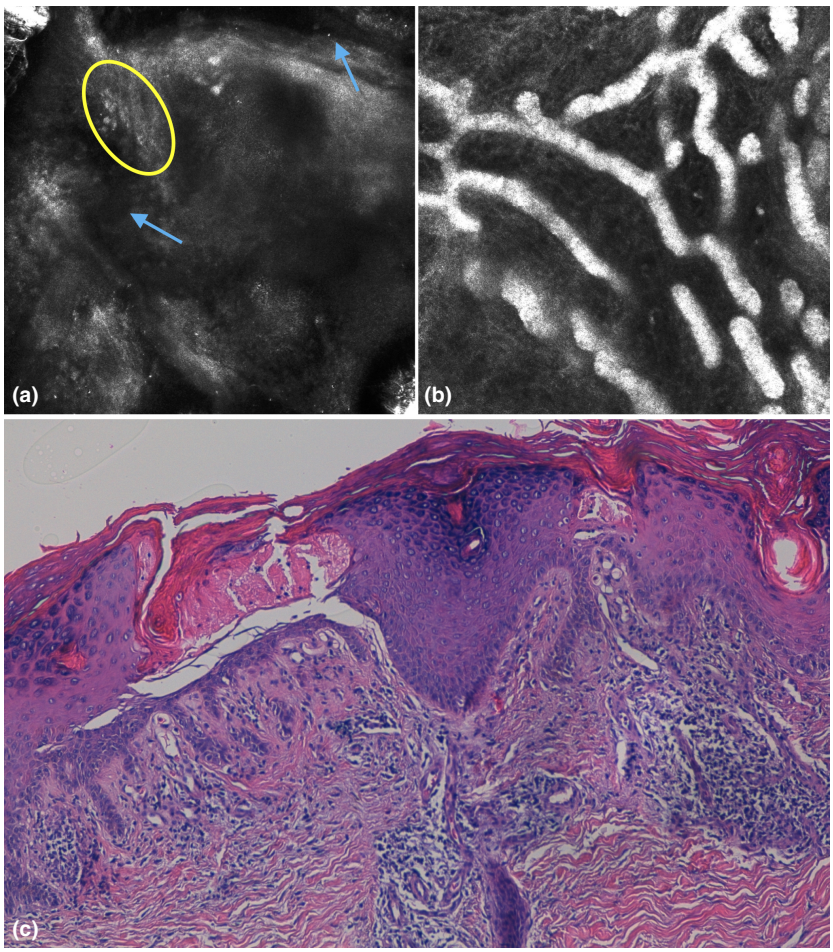

Figure 2 Galli-Galli disease – reflectance confocal microscopy appearance and histopathological examination. (a) Reflectance confocal microscopy imaging of a hyperkeratotic papule (leg): basic image (0.5 × 0.5 mm) at epidermal level reveals focal dark clefts (blue arrows) with multiple bright, roundish cells within (yellow circle). (b) Reflectance confocal microscopy imaging of a lentigo-like macule (chest): basic image (0.5 × 0.5 mm) at dermal–epidermal junction shows multiple, branched, deer antler-like highly refractile structures. (c) Histopathological examination: foci of suprabasal acantholysis with few dyskeratotic keratinocytes within, hyperkeratosis, and digitate downgrowth of branched rete ridges with basal hyperpigmentation (hematoxylin–eosin, ×100). Suprabasal acantholysis and dyskeratotic keratinocytes correlate well to dark clefts and round bright cells seen in RCM, respectively, while elongated rete ridges show an excellent correlation to confocal deer antler-like bright structures. Reflectance confocal microscopy: VivaScope1500®, Caliber: imaging and diagnostics, Rochester, NY, USA

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Figure 1 The clinical findings of the present case. The swelling developed on the lips

A case of idiopathic angioedema exacerbated by angiotensin receptor blocker administration

A 70-year-old Japanese man came to our clinic with swelling of the lips (Fig. 1), dyspnea, and hoarseness which started to develop a day prior to our examination without any apparent triggers. One month earlier, swelling of the right cheek was noted after dental therapy, and this swelling had waxed and waned for a week. These symptoms started to appear 2 years prior. The patient had a history of hypertension, and the angiotensin receptor blocker (ARB) irbesartan had been used for 2 years. We first diagnosed the eruption as idiopathic angioedema, and the administration of intravenous betamethasone sodium phosphate (4 mg/d), oral olopatadine hydrochloride (10 mg/d), and loratadine (10 mg/d) was started which resolved all the symptoms in 5 days. However, focal swelling on the face and lips appeared every 2–3 months thereafter. Laboratory tests did not show C1-inhibitor deficiency (C1-INH of 93%; normal range: 70–130%). No information was available about C1q and C4. We suspected that the eruptions might have been induced by ARB.[1,2] After the irbesartan was changed to the calcium blocker cilnidipine, development of angioedema was reduced but still appeared about three times a year. We finally diagnosed the present case as idiopathic angioedema which was exacerbated by ARB.

Angioedema usually presents as abrupt nonpitting edema of the skin and mucous membrane, commonly involving the face and oral mucosa. Angioedema usually regresses after 24–72 hours, but it may last for up to 7 days. The symptoms of angioedema are induced by increased vascular permeability in the subcutaneous tissue and/or deep dermal layer because of histamine release by mast cells or accumulation of the bradykinin in the tissue. In the histaminergic type, the angioedema usually occurs concomitant with urticaria, which favorably responds to treatment with antihistamines and corticosteroids.[3] On the other hand, bradykinin-induced angioedema, such as C1-INH deficiency, does not usually show urticaria. Antihistamines and corticosteroids are ineffective in most cases of bradykinin-induced angioedema,[4] and the selective bradykinin B2 receptor icatibant was reported to be effective in such cases.[5] Regarding the clinical manifestations, it should be noted that urticaria-like erythema may develop in bradykinin-induced angioedema[6]; thus, the presence of urticarial lesions cannot exclude the diagnosis of bradykinin-induced angioedema. In our case, administration of intravenous corticosteroid and oral antihistamines resolved symptoms. The lips and periorbital area are the most common regions of angioedema, followed by the extremities and the genitalia.[7] Angioedema is associated with various causative factors, such as allergies, hereditary or acquired compliment C1 inhibitor deficiency, and autoimmunity.[4] Angioedema may also be associated with drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) and antihypertensive drugs. Angiotensin-converting enzyme inhibitor (ACE-I) is known to be a particularly major causative drug for angioedema, whose incidence is reported to be 0.2–2.5% in patients receiving ACE-I.[8–10] ACE is known to degrade bradykinin; thus, inhibition of ACE by ACE-I results in increased bradykinin. The increased bradykinin induces aberrant expressions of C-GMP and nitric oxide through the B2 receptor in vessels,[4] resulting in vasodilatation and increased vascular permeability.

